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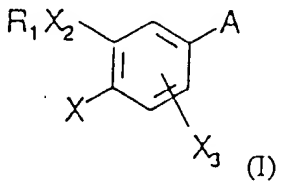
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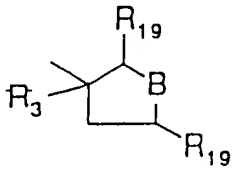
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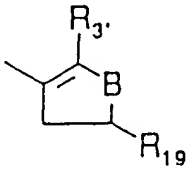
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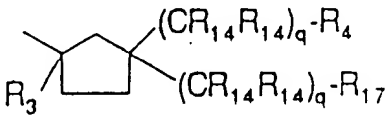
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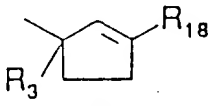
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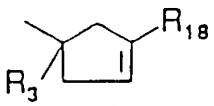
(e)

(57) Abstract

Compounds illustrated by general formula (I) useful as PDE IV inhibitors and for inhibiting the production of Tumor Necrosis Factor (TNF) are disclosed herein. In formula (I) R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens; C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group; C_{4-6} cycloalkyl containing one or two unsaturated bonds; C_{7-11} polycycloalkyl, $-(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_m-R_{10}$, $-(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_r-R_{11}$, $-(CR_{14}R_{14})_xOH$, $-(CR_{14}R_{14})_sO(CR_{14}R_{14})_m-R_{10}$, $-(CR_{14}R_{14})_sO(CR_{14}R_{14})_r-R_{11}$, $-(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$, $-(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_r-R_{11}$, $-(CR_{14}R_{14})_y-R_{11}$ or $-(CR_{14}R_{14})_z-R_{10}$; X_2 is O or NR_{14}; X_3 is hydrogen or X; X is YR_2, halogen, nitro, $NR_{14}R_{14}$ or formamide; Y is O or S(O)m; R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 5 fluorines; A is (a), (b), (c), (d) or (e); B is $>C=Z$ or $C=S$.

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CYCLOPENTANE AND CYCLOPENTENE DERIVATIVES WITH ANTIALLERGIC ANTIINFLAMMATORY AND TUMOR NECROSIS FACTOR INHIBITING ACTIVITY

Field of Invention

The present invention relates to novel cyclopentane and cyclopentene derivatives, pharmaceutical compositions containing these compounds and their use in treating allergic and inflammatory diseases, and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

It is now understood that the symptoms of chronic asthma are the manifestations of three distinct processes: 1) an early response to antigen, 2) a delayed or late response to antigen, and 3) chronic inflammation and airway hyperreactivity. Cockcroft, Ann. Allergy 55:857-862, 1985; Larsen, Hosp. Practice 22:113-127, 1987.

The agents currently available (b-adrenoceptor agonists, steroids, methylxanthines, disodium cromoglycate) are inadequate to control the disease; none of them modify all three phases of asthma and nearly all are saddled with limiting side effects. Most importantly, none of the agents, with the possible exception of steroids, alter the course of progression of chronic asthma.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs (Robison et al., Cyclic AMP Academic Press, New York, pgs. 17-47, 1971; Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, pgs. 17-29, 1973). When the appropriate agonist binds to specific cell sulface receptors, adenylate cyclase is activated which converts Mg^{2+}-ATP to cAMP at an accelerated rate. The actions of cAMP are terminated by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-AMP, an inactive metabolite.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway sooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit PDE should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cyclic AMP breakdown in airway smooth muscle and inflammatory cells. Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd. (1989). Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production is implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sacroidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

TNF has been implicated in various roles with the human acquired immune deficiency syndrome (AIDS). AIDS results from the infection of T lymphocytes with

Human Immunodeficiency Virus (HIV). It has now been discovered that monokines, specifically TNF, are implicated in the infection of T lymphocytes with HIV by playing a role in maintaining T lymphocyte activation. Furthermore, once an activated T lymphocytes is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. It has also been discovered that monokines, specifically TNF, are implicated in activated T cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by ihibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

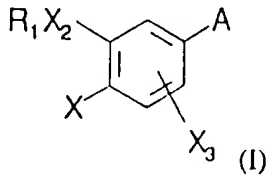
It has now been discovered that monokines are implicated in certain disease-associated problems such as cachexia and muscle degeneration. Therefore, interference with monokine activity, such as by inhibition of TNF production, in an HIV-infected individual aids in enhancing the quality of life of HIV-infected patients by reducing the severity of monokine-mediated disease associated problems such as cachexia and muscle degeneration.

TNF is also associated with yeast and fungal infections. Specifically Candida Albicans has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, Vol. 58, No. 9, p. 2750-54 (1990); and Jafari et al., Journal of Infectious Diseases, Vol. 164, p. 389-95 (1991). See also Wasan et al., Antimicrobial Agents and Chemotherapy, Vol. 35, No. 10, p. 2046-48 (1991) and Luke et al., Journal of Infectious Diseases, Vol. 162, p. 211-214 (1990)].

The discovery of a class of compounds which inhibit the production of TNF will provide a therapeutic approach for the diseases in which excessive, or unregulated TNF production is implicated.

Summary of the Invention

The compounds of this invention are illustrated by the Formula (I)



(I)

wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens; C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group; C_{4-6} cycloalkyl containing one or two unsaturated bonds; C_{7-11} polycycloalkyl, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_m$-R_{10}, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_xOH$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_y$-$R_{11}$ or -$(CR_{14}R_{14})_z$-R_{10};

X_2 is O or NR_{14};

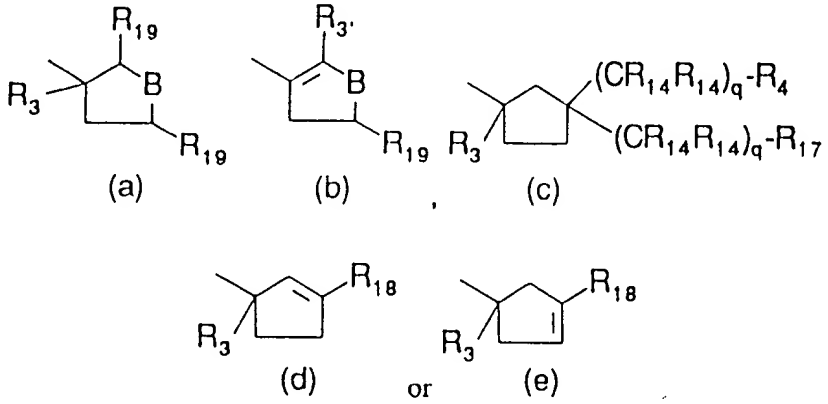
X_3 is hydrogen or X;

X is YR_2, halogen, nitro, $NR_{14}R_{14}$ or formamide;

Y is O or S(O)m;

R_2 is -CH_3 or -CH_2CH_3, each may be unsubstituted or substituted by 1 to 5 fluorines;

A is:



(a) (b) (c) (d) or (e)

B is >C=Z or C=S;

R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, OR_5, -CH_2OR_5, -NR_5R_{16}, -$CH_2NR_5R_{16}$, -$C(O)OR_5$, -$C(O)NR_5R_{16}$, -$CH=CR_9R_9$, -$C\equiv CR_9$ or -C(Z')H;

$R_{3'}$ is hydrogen, halogen, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, -CN, $-CH_2OR_5$, $-CH_2NR_8R_{16}$, $-C(O)OR_5$, $-C(O)NR_8R_{16}$ or -C(Z)H;

Z is O, $NR_{8'}$, NOR_8, NCN, NNR_8R_{16}, $C(-CN)_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_8R_{16}$, $C(-CN)NO_2$, $C(-CN)C(O)OR_{12}$ or $C(-CN)C(O)NR_8R_{16}$;

Z' is O, NR_{12}, NOR_5, NCN, $C(-CN)_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_5R_5$, $C(-CN)NO_2$, $C(-CN)C(O)OR_{12}$ or $C(-CN)C(O)NR_5R_5$;

R_4 is E or Q;

E is OR_8, $OC(O)R_8$, $OC(O)NR_5R_8$, $OS(O)_2NR_5R_8$, $OS(O)_2R_{8'}$, SR_8, $S(O)_{m'}R_{8'}$, $S(O)_2NR_8R_{16}$, NR_8R_{16}, $NR_8C(O)R_5$, $NR_{16}C(Y')R_8$, $NR_{16}C(O)OR_{8'}$, $NR_{16}C(Y')NR_8R_{16}$, $NR_{16}S(O)_2NR_8R_{16}$, $NR_{16}C(NCN)NR_8R_{16}$, $NR_{16}S(O)_2R_{8'}$, $NR_{16}C(CR_5NO_2)NR_8R_{16}$, $NR_{16}C(NCN)SR_{12}$, $NR_{16}C(CR_5NO_2)SR_{12}$, $NR_{16}C(NR_{16})NR_8R_{16}$, $NR_{16}C(O)C(O)NR_8R_{16}$, $NR_{16}C(O)C(O)OR_8$ or $NR_{16}C(O)NR_{16}S(O)_2$(4-methylphenyl);

Q is $C(Y')R_8$, $C(O)OR_8$, $C(Y')NR_8R_{16}$, $C(CR_5NO_2)NR_8R_{16}$, $C(CR_5NO_2)SR_{12}$, $C(NR_8)NR_8R_{16}$, CN, $C(NOR_5)R_8$, $C(NOR_8)R_5$, $C(NR_5)NR_8R_{16}$, $C(NR_8)NR_5R_5$, $C(NCN)NR_8R_{16}$, $C(NCN)SR_{12}$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4- or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4- or 5-thiazolidinyl) or (2-, 4- or 5-imidazolidinyl), wherein all of the heterocylic ring systems may be optionally substituted, where possible, one or more times by $R_{8'}$;

Y' is O or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, $-C(O)R_5$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-C(NCN)S(R_{12})$ or $-C(NCN)NR_5R_{16}$;

R_7 is OR_5, $-NR_5R_{16}$ or R_{12};

R_8 is hydrogen or $R_{8'}$;

$R_{8'}$ is $-(CR_{14}R_{14})_m$-D;

D is C_{1-6} alkyl, phenyl, (2-, 3- or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl) or (4- or 5-thiazolyl), triazolyl, quinolinyl or naphthyl all of which may be unsubstituted or substituted by one or more: Br, F, Cl, NR_5R_{16}, NR_6R_{16}, NO_2, $-COR_7$, $-S(O)_mR_{12}$, CN, OR_5, $-OC(O)NR_5R_{16}$, (1- or 1-(R_5)-2-imidazolyl), $-C(NR_{16})NR_5R_{16}$, $-C(NR_5)-SR_{12}$, $-OC(O)R_5$, $-C(NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}-C(O)-R_{15}$, oxazolyl, thiazolyl,

pyrazolyl, triazolyl or tetrazolyl, or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_9 is hydrogen, F or R_{12};

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted aryloxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrofuranyl, 3-tetrahydrothienyl, C_{3-6} cycloalkyl or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is -C(O)C_{1-4} alkyl, unsubstituted or substituted by one or more halogens, oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5, or when R_8 and R_{16} are as NR_8R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_{17} is R_5 or Q;

R_{18} is Q, $S(O)_2R_8'$, OR_8', $OC(O)NR_8R_{16}$ or NR_8R_{16};

each R_{19} is independently hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, OR_5, -CH_2OR_5, -NR_5R_{16}, -$CH_2NR_5R_{16}$, -C(O)OR_5, -C(O)NR_5R_{16}, -CH=CR_9R_9, -C≒CR_9 or -C(Z)H;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

s is an integer from 2 to 4;

x is an interger from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

provided that

1) when R_{10} is OH in $-(CR_{14}R_{14})_n-C(O)O-(CR_{14}R_{14})_m-R_{10}$, $-(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$ or $-C(R_{14}R_{14})_sO(CR_{14}R_{14})_m-R_{10}$, then m is 2;

2) that when X_2 is O, R_3 is hydrogen and B is >C=O or >C=S, then one of the two R_{19} terms in radical (a) of term A is not hydrogen;

3) when X_2 is O, R_3 is hydrogen and B is >C=O or >C=S, then either $R_{3'}$ or R_{19} in radical (b) of term A is not hydrogen;

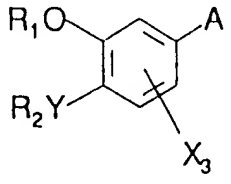
4) when X_2 is O, R_{17} is hydrogen, both of the q terms are zero and R_4 is OH, OC_{1-6}alkyl or SC_{1-6}alkyl in radical (c) of term A, then R_3 is other than hydrogen;

5) when term A is radical (c), Q is CN and both of the q terms are zero, then R_4 is not OH, SH or NR_8R_{16}; or

a pharmaceutically acceptable salt thereof.

The invention further provides for the novel compositions of the compounds of Formula I.

The compounds of Formula Ia, a subgroup of Formula I, have activity as PDE IV inhibitors. Therefore, this invention provides a method of inhibiting PDE IV which comprises administering to a subject in need thereof a compound of the Formula (Ia):



(Ia)

wherein:

R_1 is phenyl, benzyl or C_{1-2} alkyl unsubstituted or substituted by 1 or more fluorines; C_{4-6} cycloalkyl, CH_2-cyclopentyl, CH_2-cyclopropyl, C_{7-11} polycycloalkyl, 3-tetrahydrofuranyl, cyclopentenyl, $-(CH_2)_nC(O)-O-(CH_2)_m-CH_3$, $-(CH_2)_{2-4}OH$, $-(CH_2)_sO(CH_2)_m-CH_3$, $-(CH_2)_n-(C(O)NR_{14})-(CH_2)_m-CH_3$, all of which may be substituted by 1 to 3 methyl groups or one ethyl group;

X_3 is hydrogen or X;

X is YR_2, halogen, nitro, $NR_{14}R_{14}$ or formamide;

Y is O or S(O)m;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 5 fluorines;

A is defined above in the definition of Formula (I);

B is >C=Z or C=S;

R_3 is hydrogen,F, CH_3, CF_3, CF_2H, CH_2F, -CN, $-CH_2OR_5$, $-C(O)OR_5$, $-C(O)NR_5R_5$, $-C\equiv CR_9$ or -C(O)H;

$R_{3'}$ is hydrogen, C_{1-3}alkyl, CF_3, CF_2H, CH_2F, -CN, $-CH_2OR_5$, $-CH_2NR_8R_{16}$, $-C(O)OR_5$, $-C(O)NR_8R_{16}$ or -C(O)H;

Z is O, $NR_{8'}$, NOR_8, NNR_8R_{16}, $C(-CN)_2$, $CR_5C(O)OR_5$, $CR_5C(O)NR_8R_{16}$, or $C(-CN)C(O)NR_8R_{16}$;

Z' is O, NR_{12} or NOR_5;

R_4 is E or Q;

E is OR_8, NR_8R_{16}, $NR_{16}C(O)R_8$, $NR_{16}C(O)OR_{8'}$, $NR_{16}C(O)NR_8R_{16}$, $NR_{16}S(O)_2NR_8R_{16}$, $NR_{16}C(NCN)NR_8R_{16}$, $NR_{16}C(CR_5NO_2)NR_8R_{16}$, $NR_{16}C(NR_{16})NR_8R_{16}$, $NR_{16}C(O)C(O)NR_8R_{16}$, $NR_{16}C(O)C(O)OR_8$ or $NR_{16}C(O)NR_{16}S(O)_2$(4-methylphenyl);

Q is $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_{16}$, $C(CR_5NO_2)NR_8R_{16}$, CN, $C(NR_5)R_8R_{16}$, $C(NCN)NR_8R_{16}$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4- or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4- or 5-thiazolidinyl) or (2-, 4- or 5-imidazolidinyl), wherein all of the heterocylic ring systems may be unsubstituted or substituted with one $R_{8'}$;

R_5 is independently hydrogen or C_{1-2}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, $-C(O)R_5$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-C(NCN)S(R_{12})$ or $-C(NCN)NR_5R_{16}$;

R_7 is OH or $-NR_5R_{16}$;

R_8 is hydrogen or $R_{8'}$;

$R_{8'}$ is $-(CH_2)_m$-D;

D is phenyl, (2-, 3- or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1- or 2-imidazolyl), (4- or 5-thiazolyl) or (2- or 3-thienyl), all of which may be unsubstituted or substituted by one or more: Br, F, Cl, NR_5R_{16}, NR_6R_{16}, NO_2, $-COR_7$, $-S(O)_mR_{12}$, CN, OR_5, $-OC(O)NR_5R_{16}$, 1 or 2-imidazolyl, $-C(NR_{16})NR_5R_{16}$, $-C(NR_5)-SR_{12}$, $-OC(O)R_5$, $-C(NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}-C(O)-R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl, or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_9 is R_5.

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is $-C(O)C_{1-4}$ alkyl, unsubstituted or substituted by one or more halogens, oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl,

imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5, or when R_8 and R_{16} are as NR_8R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_{17} is R_5 or Q;

R_{18} is Q, $OR_{8'}$ or NR_8R_{16};

R_{19} is independently hydrogen, F, C_{1-3}alkyl, CF_3, CF_2H, CH_2F, -CN, $-CH_2OR_5$, $-C(O)OR_5$, $-C(O)NR_5R_5$, $-C\equiv CR_9$ or -C(O)H;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

s is an integer from 2 to 4;

x is an interger from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

provided that

1) that when R_3 is hydrogen and B is >C=O or >C=S, then one of the two R_{19} terms in radical (a) of term A is not hydrogen;

2) when R_3 is hydrogen and B is >C=O or >C=S, then either $R_{3'}$ or R_{19} in radical (b) of term A is not hydrogen;

3) when R_{17} is hydrogen, both of the q terms are zero and R_4 is OH or OC_{1-6}alkyl in radical (c) of term A, then R_3 is other than hydrogen;

4) when term A is radical (c), Q is CN and both of the q terms are zero, then R_4 is not OH, SH or NR_8R_{16};

5) when term A is radical (c) and one of R_4 or R_{17} is hydrogen, the other is not hydrogen; or

a pharmaceutically acceptable salt thereof.

Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticardia, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophillic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus, (Kidney Int. 37:362, 1990; Kidney Int. 35:494, 1989) and central nervous system disorders such as depression and multi-infarct dementia.

These compounds can also be used to treat a human afflicted with a human immunodeficiency virus (HIV), AIDS Related Complex (ARC) or any other disease state associated with an HIV infection, which comprises administering to such a human an effective TNF inhibiting amount of a compound of Formula (I).

The present invention also provides a method of preventing a TNF mediated disease state in an animal in need thereof, including humans, by prophylactically administering an effective amount of a compound of Formula I.

The compounds of the present invention are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo. The viruses contemplated for treatment herein are those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as, Herpes Zoster and Herpes Simplex.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo. A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of the Formula (I) may be administered in conjunction with other drugs of choice, either simultaneously or in a consecutive manner, for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidaozles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The preferred organism for treatment is the *Candida* organism. The compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of the Formula (I) to a mammal in need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Compounds of formula (I) may also be used in in treating animals. TNF mediated diseases exist in animals, including commercially important livestock and pets populations, particularly as regards viral infections. Examples of such viruses include

feline immunodeficiency virus (FIV) and other retroviruses such as equine infectious anemia visus, caprine arthritis virus, visna virus, maedi virus, and other lentiviruses.

In a further aspect, this invention relates to a composition comprising a compound of formula I in admixture with a carrier. Of particular interest is a composition comprising a compound of formula I and a pharmaceutically acceptable carrier.

Detailed Description of the Invention

All defined alkyl groups can be straight or branched.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

The term "halogen" is used to mean chloro, fluoro, bromo or iodo.

The term "cycloalkyl" as used herein includes groups of 3-6 carbon atoms such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

By the term "aryl" or "aralkyl", unless specified otherwise, as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

Examples of C_{7-11} polycycloalkyl are bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo [5.2.1.$0^{2,6}$]decyl, etc., additional examples of which are described in Saccamano et al., WO 87/06576, published 5 November 1987 whose disclosure is incorporated herein by reference in its entirety.

Examples of rings when R_5 and R_{16} in the moiety -NR_5R_{16} together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ and S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazoly, 2-triazolyl, tetrazolyl, 2-tetrazoyl, morpholinyl, piperazinyl, or pyrrolyl ring.

Preferred compounds are those wherein R_1 is cyclopentyl, CHF_2, CH_2cyclopropyl, and cyclopentyl; X_3 is hydrogen; R_2 is CHF_2 or CH_3; A is (a), (b), (c), (d) or (e); B is >C=Z; R_3 is H, -CN, or C≡CH; $R_{3'}$ and R_{19} are independently -CN, C_{1-3}alkyl, -C(O)OR_5 or -C(O)NR_8R_{16}; Z is O, $CR_5C(O)OR_5$, NOR_8 or NNR_8R_{16}; Z' is O; E is OR_5, $NHC(O)R_5$, $NHC(O)NH_2$, $NHC(NCN)NH_2$, $NHC(O)C(O)NH_2$, or $NR_5C(O)NR_{16}S(O)_2$(4-methylphenyl); Q is $COOR_5$, $CONR_5R_5$, tetrazol-5-yl or CN; q is 0 or 1; R_{18} is Q or $OR_{8'}$; and D is phenyl or (2-, 3- or 4-pyridyl).

Especially preferred are the following compounds:

methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate;

methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate;

3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid;

4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid;

methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate;

N,N-dimethyl-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide;

N,N-dimethyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide;

N,N-dimethyl-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxylate;

3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide;

4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclo-pentene-1-carboxamide;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxamide;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylic acid;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxylic acid;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxamide;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentanecarbonitrile;

5-[3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentyl]tetrazole;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentylamine;

3-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylcyclopent-2-en-1-one;

3-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylcyclopentan-1-one;

methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-3-en-2-one carboxylate;

methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate;

3-(3-Cyclopentyloxy-4-methoxyphenyl)1-carboxylic acid;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentanecarbonitrile;

5-[3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentyl]tetrazole;

methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-3-en-2-one carboxylate;

methyl [3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-ylidine]acetate;

1-acetamido-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane;

N-(4-acetylaminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentanecarboxamide;

N-(acetylaminobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentanecarboxamide 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-(4-pyridinylmethyl)cyclopentane-1-carboxamide;

1-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate;

methyl *cis*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylate;

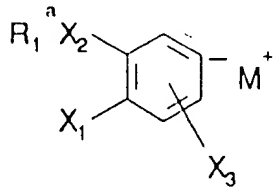
cis-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylic acid;

methyl *trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylate; and

trans-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylic acid.

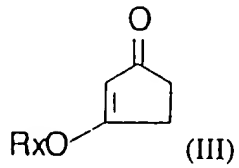
General Synthesis

The present invention provides compounds of the formula (I) which are prepared by a process comprising reacting a compound of the formula (II):



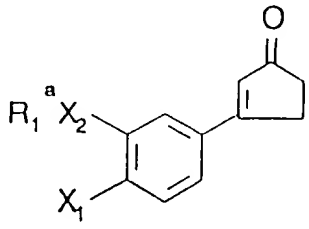
(II)

wherein X_1 and X_2 are defined in relation to formula (I), or a group convertable to X and R_1a represents R_1, as defined in relation to formula (I), or a group convertable thereto and M^+ is a counter ion, with a compound of the formula (III):



(III)

wherein OR_X is a leaving group to provide a compound of the formula (IV):



(IV)

and, thereafter, conducting one or more of the following steps in optional sequence:

(i) converting any group X_1 to X and/or $R_1{}^a$ to R_1;

(ii) appropriate manipulation of the functionality of the cyclopentenone ring of a compound of the formula (IV) to produce a compound of the formula (I). A suitable source of a counterion M^+ is an alkyl metal compound, such as a butyl lithium, optionally modified by the addition of other metal ions, such as zinc(2^+) and palladium (0). This source of counter-ion is in turn reacted with the appropriate aryl halide, such

as a bromide, to provide the compounds of formula (II). Generating and reacting compounds of the formula (II) are typically conducted in an inert solvent, such as tetrahydrofuran, at temperatures below ambient and under an inert atmosphere. Suitable leaving groups OR_X in compounds of the formula (III) are, e.g., ethoxy or isopropyloxy when M^+ is lithium, and trifluoromethylsulfonyl when zinc(2^+) and palladium (0) are also present.

Functional group manipulations of the cyclopentenone ring of a compound of the formula (IV) to produce a compound of the formula (I) are conducted by conventional procedures or modification thereof, many of which are described in the Examples.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, sublingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoro-methane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to herself a single dose.

Each dosage unit for oral administration contains suitably from 0.01 mg to 100 mg/Kg, and preferably from 1 mg to 30 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.01 mg to 100 mg, of a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof calculated as the free base. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I) or (Ia). Each dosage unit for rectal administration contains suitably 0.01 mg to 100 mg of a compound of Formula (I) or (Ia).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 1200 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit antiinflammatory activity, or if used as a TNF inhibitor, the active ingredient is administered in an amount sufficient to inhibit TNF production such that normal or subnormal levels are achieved which are sufficient to ameliorate or prevent the disease state.

The biological activity of the compounds of Formula (Ia) as in PDE IV inhibitors are demonstrated by the following tests.

Inhibitory Effect of Compounds of Formula Ia on PDE IV

I. Isolation of PDE Isozymes

Phosphodiesterase inhibitory activity and selectivity of compounds is determined using a battery of five distinct PDE isozymes. The characteristics of these PDEs appear in Table 1. The tissues used as sources of the different isozymes are as follows: 1) PDE Ia, canine trachealis; 2) PDE Ib, porcine aorta; 3) PDE Ic, guinea-pig heart; 4) PDE III, guinea-pig heart; and 5) PDE IV, human monocyte. PDEs Ia, Ib, Ic and III are partially

purified using standard chromatographic techniques (Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990). PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography (White et al., FASEB J. 4:A1987, 1990).

TABLE 1.
Characteristics of PDE Isozymes

Peak Isozyme		Km (mM)	
		cAMP	cGMP
Ia	cGMP-specific	135	4
Ib	Ca2+/calmodulin-stimulated	50	5
Ic	Ca2+/calmodulin-stimulated	1	2
	cGMP-inhibited	0.4	8
IV	Ro 20-1724-inhibited	4	38

[a] Data are from Torphy and Cieslinski, supra.
[b] Nomenclature is from Beavo, Adv. Second Messenger Phosphoprotein Res. 22: 1-38, 1988.

II. PDE Assay

Phosphodiesterase activity is assayed as described in Torphy and Cieslinski, *Mol. Pharmacol.* 37: 2206-214, 1990. The reaction is conducted in 0.1 ml of standard mixture containing (final concentrations): 50 mM Tris-HCl buffer (pH 7.5), 5 mM $MgCL_2$, 50 mM [14C]-5'AMP (approximately 400 dpm/nmole) as a carrier and for determining recovery of product, 1 mM [3H]-cAMP (approximately 2000 dpm/pmole), enzyme, and vehicle or various concentrations of test compounds. The reaction is initiated with either enzyme or substrate and conducted at 30°C. The reaction is terminated by placing reaction vessels in a 100°C heating block for 1 min. To separate cyclic nucleotide substrates from 5'-nucleotide products, 0.5 ml of 0.1 M Hepes buffer (pH 8.5) containing 0.1 M NaCl is first added to each sample. The entire sample is then applied to a polyacrylamide-boronate gel column (0.5 g of Biorad Affi-gel® 601 in a 0.7 x 10 cm Biorad® econo-column) which has been equilibrated with the 0.1 M Hepes/0.1 M NaCl buffer (pH 8.5). The unreacted cyclic nucleotides are eluted with 8 ml of equilibration buffer.

The 5'-monophosphate products are eluted with 10 ml of 0.25 M acetic acid into a scintillation vial containing 10 ml of scintillation cocktail.

Recovery of [3H]5'-AMP, as determined with the [14C]5'-AMP carrier, is 80-90%. All assays are conducted in the linear range of the reaction where less than 20% of the initial substrate is hydrolyzed. Cyclic GMP hydrolysis is assayed using a protocol identical to the one described above, with [3H]cGMP as the substrate. [3H]cGMP is used as the substrate for PDEs Ia, Ib and Ic. [3H]cAMP is used as the substrate for PDEs III and IV. IC50s for compounds of this invention range from 0.05 mM to 40 mM.

III. cAMP Accumulation in U-937 Cells

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. Approximately 2 x 106 cells in a volume of 100 ml are incubated at 37°C in a Krebs-Ringer buffer (pH 7.5) containing (mM); $CaCl_2$, 1; Hepes, 5; glucose, 1.1; Nacl, 118; KCl, 4.6; $NaHCO_3$, 24.9; KH_2PO_4, 1; BSA, 0.2 mg/ml. Cells are treated with various concentrations of test compounds (PDE inhibitors) for 1 min before the addition of a threshold concentration of PGE2 (0.1 mM). Four minutes after the addition of PGE_2, the reaction is stopped with 100 ml of 17.5% $HClO_4$ and then neutralized with 150 ml of 1 M K_2CO_3. 550 ml of sodium acetate buffer (pH 6.8) is then added to the neutralized solution. Permeabilized cells and cell debris are removed from the soluble fraction via centrifugation (1800 x g for 5 min). The supernatant is then assayed for cAMP via radioimmunoassay using commercially available kits (Dupont/New England Nuclear, Cambridge, MA). The effects of test compounds are compared to those of racemic rolipram, which is used as a standard in all experiments. Data are expressed as both an EC_{50} for increases in cAMP accumulation as a percentage of the maximum response to rolipram produced by 10 mM of the test compounds. EC_{50}s for compounds of this invention range from 0.3 mM to >10 mM.

Inhibitory Effect of Compounds of Formula (I) on
in vitro TNF Production by Human Monocytes

Section I: Assay set-up

The effects of compounds of Formula (1) on the in vitro production of TNF by human monocytes was examined using the following protocol.

Human peripheral blood monocytes were isolated and purified from either blood bank buffy coats or platletpheresis residues, according to the procedure of Colotta, R. et al., *J. Iolmmunol.*, 132(2):936 (1984). The monocytes were plated at a density of 1 x 106 cells/ml medium/well in 24-well multi-dishes. The cells were allowed to adhere for 1 hour after which time the supernatant was aspirated and 1 ml fresh medium (RPMI-1640 Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum and

penicillin and streptomycin at 10 units/ml was added. The cells were incubated for 45 minutes in the presence or absence of test compounds at 1 nM-10 um dose ranges (compounds were solubilized in Dimethylsulfoxide/Ethanol such that the final solvent concentration in the culture medium was 0.5% Dimethyl sulfoxide/0.5% Ethanol). Bacterial lipopolysaccharide (E. coli 055:B5[LPS] from Sigma Chemicals Co.) was then added at 100 ng/ml in 10 ml Phosphate Buffered Saline (PBS) and cultures incubated for 16-18 hours at 37°C in a 5% CO2 incubator. At the end of the incubation period, culture supernatants were removed from the cells, centrifuged at 3000 revolutions per minute (rpm) to remove cell debris and .05 ml of the supernatant assayed for the TNF activity using the radioimmunoassay described below.

Section II: Radioimmunoassay procedure for TNF activity

The assay buffer consisted of 0.01 M $NaPO_4$, 0.15M NaCl, 0.025M EDTA and 0.1% sodium azide at pH 7.4. Human recombinant TNF (rhTNF) obtained using the procedure of Chen et al., Nature, 330:581-583 (1987) was iodinated by a modified Chloramine-T method described in Section III below. To samples (50 ml culture supernatants) or rhTNF standards, a 1/9000 dilution of polyclonal rabbit anti-rhTNF (Genzyme, Boston, MA) and 8000 cpm of 125I-TNF was added in a final volume of 400 ml buffer and incubated overnight (18 hours) at 4°C. Normal rabbit serum and goat anti-rabbit IgG (Calbiochem) were titered against each other for maximum precipitation of the anti-rhTNF. The appropriate dilutions of carrier normal rabbit serum (1/200), goat anti-rabbit IgG (1/4) and 25 Units heparin (Calbiochem) were allowed to precipitate about 200 µl of this complex was added per assay tube and incubated overnight at 4°C. Tubes were centrifuged for 30 minutes at 2000 rpm, supernatants were carefully aspirated, and radioactivity associated with the pellets measured in a Beckman Gamma 5500 counter. The logit-log linear transformation curve was used for the calculations. The concentrations of TNF in the samples were read off a standard curve of rhTNF that was linear in the 157 to 20,000 pg/ml range.

Section III: Radioiodination of rhTNF

Iodination of rhTNF was performed using a modified chloramine-T method of Frolik et al., J. Biol. Chem., 259:10995-11000 (1984). Briefly, 5 mg of rhTNF in 5 ml of 20 mM Tris pH 7.5, was diluted with 15 ml of 0.5M KPO4 and 10 ml of carrier free 125I(100mCi/ml; ICN). To initiate the reaction, a 5 ml aliquot of a 200 mg/ml (aqueous) chloramine-T solution is added. After 2 minutes at room temperature, an additional 5 ml aliquot was added followed 1.5 minutes later by a final 5 ml addition of chloramine-T. The reaction was stopped 1 minute later by sequential addition of 20 ml of 50 mM Sodium Metabisulfite, 100 ml of 120 mM Potassium Iodide and 200 ml of 1.2 mg/ml Urea. The contents were mixed and the reaction mixture was passed over a pre-packed Sephadex G-25 column (PD 10 Pharmacia), equilibrated and eluted with

Phosphate Buffered Saline pH 7.4 containing 0.25% gelatin. The peak radioactivity containing fractions were pooled and stored at -20°C. Biological activity of iodinated TNF was measured by the L929 cytotoxicity assay of Neale, M.L. et al., Eur. J. Can. Clin. Oncol., 25(1):133-137 (1989).

Section IV: Measurement of TNF-ELISA

Levels of TNF were also measured using a modification of the basic sandwich ELISA assay method described in Winston et al., Current Protocols in Molecular Biology, Page 11.2.1, Ausubel et al., Ed. (1987) John Wiley and Sons, New York, USA. The ELISA employed a murine monoclonal anti-human TNF antibody, described below, as the capture antibody and a polyclonal rabbit anti-human TNF, described below, as the second antibody. For detection, a peroxidase-conjugated goat anti-rabbit antibody (Boehringer Mannheim, Indianapolis, Indiana, USA, Catalog #650222) was added followed by a substrate for peroxidase (1 mg/ml orthophenylenediamine with 0.1% urea peroxide). TNF levels in samples were calculated from a standard curve generated with recombinant human TNF produced in *E. coli* (obtained from SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA).

Section V: Production of anti-human TNF antibodies

Monoclonal antibodies to human TNF were prepared from spleens of BALB/c mice immunized with recombinant human TNF using a modification of the method of Kohler and Millstein, Nature 256:495 (1975), the entire disclosure of which is hereby incorporated by reference. Polyclonal rabbit anti-human TNF antibodies were prepared by repeated immunization of New Zealand White (NZW) rabbits with recombinant human TNF emulsified in complete Freund's adjuvant (DIFCO, IL., USA).

Endotoxin Shock in D-gal-Sensitized Mice

The protocol used to test the compound of the method of the subject invention was essentially as has been described in Galanos et al., Proc. Nat'l. Acad. Sci. USA, 76:5939-43 (1979) whose disclosure is herein incorporated by reference. D-gal f(D(+)Galactosidase) sensitizes various strains of mice to the lethal effects of endotoxin. The administration of D-gal (300-500 mg/kg) intravenously (i.v.) sensitizes the mice to doses of lipopolysaccharide (LPS) as low as 0.1 g. Male C5BL/6 mice, obtained from Charles River Laboratories (Stone Ridge, New York, USA) of 6-12 weeks of age were injected i.v. with 0.1 g of LPS from Salmonella typhosa *Difco Laboratories, Detroit, Michigan, USA) admixed with D(+)gal (Sigma; 500 mg/kg) in 0.20-0.25 ml pyrogen-free saline. Compounds to be tested were administered at various times prior to or following the i.v. injection of LPS/D-gal. In this model, the control animals usually die 5-6 hours following the injection of LPS, although on occasion deaths were seen between 24 and 48 hours.

Measurement of TNF Activity

Plasma levels of TNF were measured using a modification of the basic sandwich ELISA method described in Winston et al., Current Protocols in Molecular Biology, Pg. 11.2.1, Ausubel et al., Ed. (1987) John Wiley and Sons, New York, USA. The ELISA employed a hampster monoclonal anti-mouse TNF (Genzyme, Boston, MA, USA) as the detecting antibody. TNF levels in mouse samples were calculated from a standard curve generated with recombinant murine TNF (Genzyme, Boston, MA, USA). TNF levels determined by ELISA correlated with levels detected by the L929 bioassay of Ruff et al., J. Immunol. 125:1671-1677 (1980), with 1 Unit of activity in the bioassay corresponding to 70 picograms (pg) of TNF in the ELISA. The ELISA detected levels of TNF down to 25 pg/ml.

The following examples illustrate how to make compounds and formulations containing same. These are examples and as such are intended in no way to limit the scope of the invention or the appended claims.

EXAMPLE 1

3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one

To a solution of 4-bromo-2-cyclopentyloxy-1-methoxybenzene 9.50 g, 35.0 mmol) in tetrahydrofuran (70 ml) at -78°C under an argon atmosphere was added dropwise *n*-butyllithium (15 ml of 2.5M solution, 37.5 mmol). The resulting mixture was stirred at -78°C for 1.25 hr and added dropwise to a cooled solution (0°C) of 3-isopropoxy-2-cyclopentenone (4.95 g, 35.3 mmol) in tetrahydrofuran (20 ml). Upon completion of the addition, the reaction mixture was allowed to warm to room temperature and was stirred for 1.5 hr. Hydrochloric acid (70 ml of 0.6N solution) was added to the reaction mixture and stirring was continued for 2.5 hr. The reaction mixture was poured into water and extracted with methylene chloride (four times). The combined organic extracts were dried (magnesium sulfate), the solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with 1:4:5 methylene chloride/ether/hexanes. Recrystallization from methylene chloride/ether/hexanes provided needles : m.p. 136-137°C. Analysis: Calc. for $C_{17}H_{20}O_3$: C74.97, H7.40; found: C74.96, H7.32.

EXAMPLE 2

Methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate and Methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate

2a) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-cyclopentyltrifluoromethylsulfonate. To a solution of diisopropylamine (1.2 mL, 8.56 mmol) in tetrahydrofuran (12 mL) at 0°C under an argon atmosphere was added n-butyllithium (3.4 mL of 2.5 M solution, 8.5 mmol) and the resulting solution was stirred for 15 min and cooled to -78°C. To this was added a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-one (2.12 g, 7.73 mmol) in tetrahydrofuran (2.5 mL). The resulting mixture was stirred at -78°C for 2 h at which time N-phenyltrifluoromethylsulfonamide (3.04 g, 8.5 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 5 h. The mixture was poured into water and extracted with ether. The organic extract was dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 20% ether/hexanes to afford a light green oil.

2b) Methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate and Methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate. To a solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentenyl trifluoromethylsulfonate (268 mg, 0.66 mmol) in 1:1 methanol/N,N-dimethylformamide (4 mL) were added triethylamine (0.19 mL, 1.38 mmol) and tetrakis(triphenylphosphine)palladium (38 mg, 0.03 mmol). The resulting mixture was stirred under a carbon monoxide atmosphere for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography, eluting with 20% ether/hexanes to provide a mixture of unsaturated esters. Analysis Calc. for $C_{19}H_{24}O_4$: C 72.13, H 7.65; found: C 71.49, H 7.61.

EXAMPLE 3

3-(3-Cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid and 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid

To a solution containing a mixture of methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate and methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate (79 mg, 0.25 mmol) in methanol (2 mL) was added a solution of potassium hydroxide (48 mg of 86% purity, 0.76 mmol) in water (0.3 mL). The resulting mixture was stirred at room temperature for 6 h. The mixture was acidified to pH 3 with dilute aqueous hydrochloric acid and extracted with methylene chloride. The organic extract was dried (magnesium sulfate) and the solvent was removed in vacuo to provide an oil.

EXAMPLE 4

Methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentane-1-carboxylate

To a solution containing a mixture of methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate and methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate (115 mg, 0.36 mmol) in ethanol (6 mL) was added 10% palladium on activated carbon (40 mg) and the resulting mixture was hydrogenated at 60 psi for 3 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 20% ethane/hexanes to provide the saturated ester. Analysis Calc. for $C_{19}H_{26}O_4$: C 71.67, H 8.23; found: C 71.39, H 8.12.

EXAMPLE 5

N,N-Dimethyl-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide and N,N-Dimethyl0-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide

N,N-Dimethyl-3-(c-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide and N,N-dimethyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide. To a solution of (3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentenyl trifluoromethylsulfonate (290 mg, 0.71 mmol) in N,N-dimethylformamide (6 mL) was added tetrakis(triphenyl-phosphine)palladium (60 mg, 0.05 mmol) followed by dimethylamine (3 mL of 40% aqueous solution, 23.7 mmol). The resulting mixture was stirred under a carbon monoxide atmosphere for 5 h. The mixture was concentrated under reduced pressure and the residue was partitioned between methylene chloride and water. The organic extract was dried (sodium sulfate) and the solvent was removed in vacuo. The residue was purified by flash chromatography, eluting with 10% methylene chloride/ether to obtain an orange oil. This was further purified by flash chromatography, eluting with 1:3:6 methylene chloride/hexanes/ether to provide a pale yellow oil. Analysis Calc. for $C_{20}H_{26}NO_3$: C 72.92, H 8.26, N 4.25; found: C 71.57, H 8.25, N 4.40.

EXAMPLE 6

Dimethyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentane-1,1-dicarboxylate

To a cooled (0°C) solution of diisopropylamine (90 mL, 0.64 mmol) in anhydrous tetrahydrofuran (3 mL) under an argon atmosphere was added n-butyl lithium (0.25 mL of 2.5 M solution, 90.63 mmol). The resulting solution was stirred at 0°C for 15 min and then cooled to -78°C. To this was added a solution of methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentane-1-carboxylate (171 mg, 0.54 mmol) in tetrahydrofuran (0.5 mL). The resulting mixture was stirred at -78°C for 45 min, at

which time methyl chloroformate (50 mL, 0.65 mmol) was added. The reaction mixture was stirred at -78°C for 1 h and then allowed to warm to room temperature. Aqueous ammonium chloride was added and the mixture was extracted with ether. The ether extract was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 20% ether/hexanes to provide the diester as an oil. Analysis Calc. for $C_{21}H_{28}O_6$: C 67.00, H 7.50; found : C 66.29, H 7.51.

EXAMPLE 7

3-(3-Cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide and 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide

To a solution containing a mixture of 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid and 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid (500 mg, 1.65 mmol) in N,N-dimethylformamide (5mL) under an argon atmosphere was added N-methylmorpholine (0.21 mL, 1.91 mol). The solution was cooled to -15°C and isobutyl chloroformate (0.25 mL, 1.89 mmol) was added. The resulting mixture was stirred at -15°C for 20 min. Concentrated ammonium hydroxide (0.20 mL, 3.0 mmol) was added and the mixture was allowed to warm to room temperature. After stirring for 1.5 h, the mixture was partitioned between methylene chloride and water. The organic extract was dried (magnesium chloride) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting first with 30% methylene chloride/ether followed by 5% ether/methanol to provide an oil which crystallized upon standing. The crystals were filtered and washed with ether: m.p. 139-141°C. Analysis Calc. for $C_{18}H_{23}NO_3$: C 71.73, H 7.69, N 4.65; found : C 71.91, H 7.84, N 4.75.

EXAMPLE 8

3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxamide

To a solution containing a mixture of 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide and 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide (318 mg, 1.06 mmol) in ethanol (17 mL) was added 10% palladium on activated carbon (110 mg) and the resulting mixture was hydrogenated at 60 psi for 4.5 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 0.5:1.5:8 methanol/methylene chloride/ether to provide the saturated amide as a powder which was recrystallized from ether/methylene chloride/hexanes: m.p. 125 - 127°C. Analysis Calc. for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62; found : C 71.21, H 8.32, N 4.64.

EXAMPLE 9

3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylic acid

To a solution of methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate (354 mg, 1.11 mmol) in methanol (5 mL) under an argon atmosphere was added a solution of potassium hydroxide (210 mg of 89% purity, 3.33 mmol) in water (1 mL). The resulting mixture was stirred at room temperature for 4 h, then poured into water and extracted with ether. The aqueous phase was adjusted to pH 2 with 3 N hydrochloric acid and extracted with ether. The organic phase from the acid extraction was dried (magnesium sulfate) and concentrated under reduced pressure to provide a viscous oil which solidified upon standing. The solid was recrystallized from ether/hexanes to afford the acid: m.p. 57-58°C. Analysis Calc. for $C_{18}H_{24}O_4$: C 71.03, H 7.95; found : C 70.93, H 7.57.

EXAMPLE 10

3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxylic acid

A mixture of methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxylate (47 mg, 0.12 mmol) and potassium hydroxide (109 mg, 1.95 mmol) in 5:1 methanol/water (6 mL) was heated at 75°C for 50 h and then allowed to cool to room temperature. The mixture was acidified with concentrated hydrochloric acid and extracted with methylene chloride. The organic extract was washed with saturated aqueous sodium chloride and dried (magnesium chloride). The solvent was removed in vacuo to provide the diacid. Analysis Calc. for $C_{19}H_{24}O_6$: C 65.13, H 7.48; found : C 60.98, H 6.59.

EXAMPLE 11

3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxamide

To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxylic acid (280 mg, 0.74 mmol) in methanol (10 mL) was added sodium cyanide (9 mg, 0.18 mmol). Ammonia was introduced into the mixture, which was stirred at room temperature for 36 h. Additional ammonia was introduced and the reaction mixture was stirred at room temperature for an additional 4 d. The mixture was concentrated under reduced pressure and ether was added to the residue. Ethereal hydrochloric acid (0.5 mL of 1 M solution) was added and the mixture was concentrated under reduced pressure. The solid residue was suspended in methylene chloride and filtered. The solid was dissolved in methanol. The solvent was removed in vacuo and the residue was triturated with hexanes to provide a white solid. Analysis Calc. for $C_{19}H_{26}N_2O_4$: C 65.88, H 7.57, N 8.09; found : C 58.77, H 6.75, N 6.90.

EXAMPLE 12

3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentanecarbonitrile

To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxamide (325 mg, 1.07 mmol) in methylene chloride 2 mL) at 0°C under an argon atmosphere was added pyridine (0.18 mL, 2.2 mmol), followed by trifluoroacetic anhydride (0.17 mL, 1.18 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 4 h. The mixture was partitioned between ether and slightly acidic water. The organic extract was dried (magnesium sulfate) and the solvent was removed in vacuo. The residue was purified by flash chromatography, eluting with 1:2 ether/hexanes to provide an oil. Analysis Calc. for $C_{18}H_{23}NO_2 \cdot 1/8\ H_2O$: C 75.16, H 8.15, N 4.87; found : C 75.23, H 8.35, N 5.08.

EXAMPLE 13

5-[3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentyl]tetrazole

To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentanecarbonitrile (248 mg, 0.87 mmol) in N-methylpyrrolidinone (4 mL) under an argon atmosphere were added sodium azide (170 mg, 2.6 mmol) and triethylamine hydrochloride (179 mg, 1.3 mmol). The resulting mixture was heated at 130°C for 24 h and then allowed to cool to room temperature. The mixture was partitioned between methylene chloride and slightly acidic water. The organic extract was dried (magnesium sulfate) and the solvent was removed in vacuo. The residue was purified by flash chromatography, eluting with 0.6% acetic acid/ether. The tetrazole was isolated and was crystallized from methylene chloride/ether to give a white solid: m.p. 121-123°C. Analysis Calc. for C 65.83, H 7.37, N 17.06; found : C 65.84, H 7.62, N 17.11.

EXAMPLE 14

3-(Cyclopentyloxy-4-methoxyphenyl)cyclopentylamine

14(a/b) 3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one-anti-oxime and 3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopent-2-en-1-one-syn-oxime 3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one (681 mg, 2.5 mmol), hydroxylamine hydrochloride (681 mg, 9.8 mmol) and pyridine (3 mL, 37.4 mmol) in absolute ethanol (9 mL) was heated at reflux under argon for 4 h. The cooled mixture was partitioned between methylene chloride and water, the organic layer was washed twice with acidic water dried (magnesium sulfate) and evaporated. Flash chromatography, eluting with 2:2:1 ether/hexane/methylene chloride, provided:

14(a) 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one-anti-oxime, which was triturated with methylene chloride/ether to yield a light yellow solid: m.p. 153 - 154°C. Analysis Calc. for $C_{17}H_{21}N_2O_3$: C 71.06, H 7.37, N 4.87; found: C

71.44, H 7.06, N 4.84 and 14(b) 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one-syn-oxime, which was triturated with methylene chloride/ether to yield a pale yellow solid: m.p. 156 - 157°C.

14(c) 3-(3-Cyclopentyloxy-4-methoxyphenyl)-cyclopentylamine. A mixture of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one-anti-oxime and 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one-syn-oxime (180 mg, 0.63 mmol) with perchloric acid (0.055 mL) and 10% palladium on carbon (75 mg) in methanol (15 ml) was hydrogenated at 60 psi for 8 h. The mixture was filtered through celite, combined with the product from a similar reaction conducted on a 55 mg scale, and the filtrate was partitioned between methylene chloride and saturated aqueous sodium carbonate. After three extractions, the organic layers were dried (potassium carbonate) and evaporated to a colorless oil.

EXAMPLE 15

3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-methyl-cyclopent-2-en-1-one

To a solution of a 4-lithio-2-cyclopentyloxy-1-methoxybenzene (6.71 mmol) prepared substantially as in Example 1 was added an etheral solution of zinc chloride (1.0 M, 6.7 mL, 6.7 mmol). After 80 min, the mixture was warmed to 0°C and a solution of 2-methyl-3-trifluoro-methylsulfonylcyclopent-2-en-1-one (1.64 g, 6.7 mmol) in tetrahydrofuran (6 mL) and tetrakis(triphenylphosphine)palladium (O) (0.39 g, 3.4 mmol) was added. After 4 h at room temperature, the mixture was partitioned between ethyl acetate and water, the organic extract was washed with brine, dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 50% ether/hexanes and then with 2:1 ether/hexanes, provided an amorphous material. Analysis : Calc. for $C_{18}H_{22}O_3 \cdot 1/8\ H_2O$: C 74.91, H 7.77; found : C 74.92, H 7.31.

EXAMPLE 16

3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-methyl-cyclopentan-1-one

To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)-2-methyl-cyclopent-2-en-1-one (0.34 g, 1.2 mmol) in ethanol (30 mL) containing 2 drops of 50% aqueous sodium hydroxide was added 10% palladium on activated carbon (0.3 g) and the resulting mixture was hydrogenated at 60 psi for 6.5 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 50% ether/hexanes, to provide an amorphous material. Analysis Calc. for $C_{18}H_{24}O_3 \cdot 1/8\ H_2O$: C 74.39, H 8.41; found : C 74.38, H 8.18.

EXAMPLE 17

Methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-3-en-2-one carboxylate

To a solution of diisopropylamine (0.7 mL, 5.05 mmol) in tetrahydrofuran (25 mL) at -78°C under an argon atmosphere was added n-butyllithium (2.05 mL of 2.5 M solution, 5.13 mmol) and the resulting solution was stirred for 30 min at 0°C and recooled to -78°C. To this was added a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-2-en-1-one (0.5 g, 1.84 mmol) in tetrahydrofuran (5 mL). The resulting mixture was stirred at -78° for 2 h, at which time methyl chloroformate (0.4 mL, 5.5 mmol) was added. After 1 h, the mixture was allowed to warm to room temperature and treated with aqueous ammonium chloride. The mixture was poured into water and extracted with methylene chloride. The organic extract was washed with dilute hydrochloric acid and water, was dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 2.5% ether/methylene chloride, to afford a brown solid (0.21 g, 35%). Recrystallization from hexane/methylene chloride provided a tan solid: m.p. 126 - 127°C. Analysis Calc. for $C_{19}H_{22}O_5 \cdot 1/8\ H_2O$: C 68.61, H 6.74; found: C 68.70, H 6.64.

EXAMPLE 18

Methyl [3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-ylidine]acetate

Methyl [3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-ylidine]acetate

A mixture of trimethylphosphonoacetate (0.12 mL, 0.75 mmol) and sodium hydride (23 mg, 80% dispersion, 0.77 mmol) in dry tetrahydrofuran (5 mL) was stirred under an argon atmosphere at room temperature for 0.5h. A solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-one (0.21 g, 0.75 mmol) in dry tetrahydrofuran (2 mL) was added and the mixture was allowed to stir under an argon atmosphere at room temperature for 48h. The mixture was partitioned between water and methylene chloride, the organic extract was dried (magnesium sulfate) and the solvent is removed *in vacuo*. Purification by flash chromatography, eluting with 1:2 ether/hexanes · provided an oil.

Analysis Calc. for $C_{20}H_{26}O_4 \cdot 1/4H_2O$: C 71.72, H 7.97; found: C 71.74, H 7.92.

EXAMPLE 19

Methyl 2-[3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane]acetate

Methyl 2-[3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane]acetate A mixture of methyl [3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-ylidine]acetate ((0.14 g, 0.42 mmol) and 10% palladium on carbon (50 mg) in methanol (5 mL) was hydrogenated at 60 psi for 4h. The mixture was diluted with methylene

chloride, filtered and evaporated. Purification by flash chromatography, eluting with 1:2 ether/hexanes provided an oil.
Analysis Calc. for $C_{20}H_{28}O_4 \cdot 1/4H_2O$: C 71.29, H 8.53; found: C 71.29, H 8.53.

Example 20

2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentane]acetic acid

2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)cyclopentane]acetic acid A solution of methyl 2-[3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane]acetate (0.095 g, 1 mmol) in methanol (5 mL) was treated with a solution of potassium hydroxide (0.056 g of 89% material, 0.89 mmol) in water (1 mL) for 24h. The mixture was acidified to pH 1, was extracted with methlyene chloride, the extract was dried (magnesium sulfate) and evaporated. Trituration with ether/hexane provided a white solid: m.p. 78-80°C.
Analysis Calc. for $C_{19}H_{26}O_4$: C 71.67, H 8.23; found: C 71.35, H 8.33.

Example 21

1- Acetamido-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane

1- Acetamido-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane The title compound was prepared by acetylation of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentylamine under standard conditions: m.p. 83.5-88°C.

Example 22

N-(4-Acetylaminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentanecarboxamide,

N-(4-Acetylaminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentane-carboxamide. To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylic acid (162 mg, 0.53 mmol) in methylene chloride (3.5 mL) under an argon atmosphere was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (133 mg, 0.69 mmol), followed by 4-dimethylaminopyridine (85 mg, 0.69 mmol) and p-aminoacetanilide (105 mg, 0.69 mmol). The resulting mixture was stirred at room temperature overnight. The mixture was poured into methanol/ methylene chloride, washed with dilute aqueous hydrochloric acid and water and dried (potassium carbonate). The solvent was removed under reduced pressure and the residue was purified by flash chromatography, eluting with 5% isopropanol/ methylene chloride to provide a white crystalline solid: m.p. 146 - 147°C.
Analysis Calc. for $C_{26}H_{32}N_2O_4$: C 71.53, H 7.39, N 6.42; found : 71.13, H 7.34, N 6.24.

EXAMPLE 23

N-(Acetylaminobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentanecarboxamide

23(a) 3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(4-nitrobenzyl)cyclopentanecarboxamide To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylic acid (162 mg, 0.53 mmol) in methylene chloride (3.5 mL) under an argon atmosphere was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (132 mg, 0.69 mmol), followed by 4-dimethylaminopyridine (175 mg, 1.4 mmol) and 4-nitrobenzylamine hydrochloride (131 mg, 0.69 mmol). The resulting mixture was stirred at room temperature for 20 h. Methylene chloride was added and the mixture was washed with 10% hydrochloric acid and water and dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 1 : 1 ethyl acetate/ hexanes to provide the product as a pale yellow glassy solid.

23(b) N-(4-Aminobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentanecarboxamide To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-(4-nitrobenzyl)cyclopentane-carboxamide (175 mg, 0.36 mmol) in 1 : 1 tetrahydrofuran/ methanol (6 mL) under an argon atmosphere was added ammonium formate (317 mg, 5.02 mmol), followed by 10% palladium on activated carbon (48 mg). The resulting mixture was stirred at room temperature for 4 h, then diluted with methylene chloride and filtered through a pad of Celite. The solvent was removed *in vacuo*. The residue was dissolved in methylene chloride, washed with water and dried (magnesium sulfate). Removal of the solvent *in vacuo* provided the product as a pale yellow semi-solid.

23(c) N-(Acetylaminobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentanecarboxamide To a solution of N-(4-aminobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-carboxamide (130 mg, 0.32 mmol) in methylene chloride (2 mL) under an argon atmosphere was added pyridine (5 drops) and acetic anhydride (95 mL, 1.0 mmol). The resulting mixture was stirred at room temperature for 3 h, then partitioned between methylene chloride and water. The organic extract was washed with hydrochloric acid and water and dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 3% isopropanol/ methylene chloride to afford the product as a crystalline solid : m.p. 159 - 161°C.

Analysis Calc. for $C_{27}H_{34}N_2O_4 \cdot 1/4\ H_2O$: C 71.26, H 7.64, N 6.16; C 71.14, H 7.57, N 5.95.

EXAMPLE 24

3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(4-pyridinylmethyl)cyclopentane-1-carboxamide.

3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(4-pyridinylmethyl)cyclopentane-1-carboxamide To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylic acid (269 mg, 0.88 mmol) in N,N-dimethylformamide (5 mL) at 0°C under an argon atmosphere was added N-methylmorpholine (0.29 mL, 2.65 mmol) followed by ethyl chloroformate (0.10 mL, 1.03 mmol). The resulting mixture was stirred at 0°C for 30 min and then allowed to warm to room temperature. After stirring for 1 h at room temperature 4-aminomethylpyridine (0.18 mL, 1.76 mmol) was added and the resulting mixture was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate. The organic extract was washed with 10% hydrochloric acid and saturated aqueous sodium chloride and dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 2.5% methanol/ methylene chloride to provide an oil. This was further purified by flash chromatography, eluting first with 2% methanol/ ether followed by 5% methanol/ methylene chloride to afford a colorless oil. Analysis Calc. for $C_{24}H_{30}N_2O_3 \cdot 0.5\ H_2O$: C 71.44, H 7.74, N 6.94; found : C 71.45, H 7.60, N 7.17.

EXAMPLE 25

1-Amino-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate.

25(a) Methyl 1-azido-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate To a solution of methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate (380 mg, 1.19 mmol) in anhydrous tetrahydrofuran (20 mL) at -78°C under an argon atmosphere was added potassium hexamethyldisilazide (2.65 mL of 0.5 M solution, 1.32 mmol). The resulting mixture was stirred at -78°C for 10 min, at which time a solution of (2,4,6-triisopropylphenyl)sulfonylazide (460 mg, 1.49 mmol) in tetrahydrofuran (5 mL) was added. After stirring at -78°C for 10 min, glacial acetic acid (0.25 mL, 4.38 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was extracted with methylene chloride and the organic extract was dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 1 : 2 ether/ hexanes to provide a mixture of diastereomeric azides.

25(b) Methyl 1-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate To a mixture of the diastereomeric azides (350 mg, 0.98 mmol) in methanol (10 mL) was added 10% palladium on activated carbon (75 mg) and glacial acetic acid (0.10 mL). The resulting mixture was hydrogenated at 60 psi for 7 h. Methylene chloride was added and the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was partitioned between acidic water and ether. The aqueous phase was saturated with sodium bicarbonate and extracted with methylene chloride. The organic phase from the basic extraction was dried (potassium carbonate). The solvent was removed *in vacuo* to provide the diastereomeric mixture of amino esters as an oil.

25(c) 1-Amino-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate To a solution of methyl 1-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate (98 mg, 0.29 mmol) in methanol (5 mL) under an argon atmosphere was added a solution of sodium hydroxide (65 mg, 1.6 mmol) in water (1 mL). The resulting mixture was stirred at room temperature overnight and then poured into water (15 mL). The pH was adjusted to 5 - 6 with 3 N hydrochloric acid and the mixture was cooled to 0°C. The precipitate which formed was collected by filtration and washed with ice water (2x) and ether (2x) and dried to provide the amino acid (36 mg, 39%, decomposition at >225°C).
Analysis Calc. for $C_{18}H_{25}NO_4$: C 67.69, H 7.89, N 4.39; found: C 67.68, H 8.04, N 4.44.

EXAMPLE 26

7-(3-Cyclopentyloxy-4-methoxyphenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione.

7-(3-Cyclopentyloxy-4-methoxyphenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione A mixture of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-one (1.37 g, 5.0 mmol), sodium cyanide (270 mg, 5.5 mmol), ammonium carbonate (965 mg, 12.36 mmol) and triethylamine (0.77 mL, 5.5 mmol) in 1 : 1 dimethylsulfoxide/ 50% aqueous ethanol (40 mL) under an argon atmosphere was stirred at 50 - 60°C. After 8 h, additional ammonium carbonate (965 mg, 12.36 mmol) was added and heating was continued for an additional 15 h. The mixture was poured into water. The pH was adjusted to 4 and the mixture was extracted with methylene chloride. The organic extract was dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 10% methylene chloride/ ether to provide the product as a mixture of diastereomers.

Analysis Calc. for $C_{19}H_{24}N_2O_4$: C 66.26, H 7.02, N 8.13; found : C 66.22, H 7.20, N 8.01.

EXAMPLE 27

7-(3-Cyclopentyloxy-4-methoxyphenyl)-1,3-bis[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4,4]nonane-2,4-dione,
cis-7-(3-Cyclopentyloxy-4-methoxyphenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4,4]nonane-2,4-dione,and
trans-7-(3-Cyclopentyloxy-4-methoxyphenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4,4]nonane-2,4-dione.

27(a) 7-(3-Cyclopentyloxy-4-methoxyphenyl)-1,3-bis[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4,4]nonane-2,4-dione To a solution of 7-(3-cyclopentyloxy-4-methoxyphenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (1.4 g, 4.07 mmol) in methylene chloride (20 mL) under an argon atmosphere was added triethylamine (0.62 mL, 4.47 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol) and p-toluenesulfonyl chloride (830 mg, 4.35 mmol). The resulting mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride and acidic water. The organic extract was washed with acidic water (3x) and dried (magnesium sulfate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 40% ethyl acetate/ cyclohexane to provide the dialkylated product as a solid: m.p. 145 - 161°C. Analysis Calc. for $C_{33}H_{36}N_2O_8S_2$: C60.72, H 5.56, N 4.29, S 9.82; found : C 60.99, H 5.82, N 4.33, S 9.95.

27(b) *cis*-7-(3-Cyclopentyloxy-4-methoxyphenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4,4]nonane-2,4-dione The cis-substituted mono-alkylated product was obtained through further purification of the reaction mixture by flash chromatography, eluting with 40% ethyl acetate/ cyclohexane. Analysis Calc. for $C_{26}H_{30}N_2O_6S$: C 62.63, H 6.07, N 5.62; found : C 63.56, H 6.64, N 5.28.

27(c) *trans*-7-(3-Cyclopentyloxy-4-methoxyphenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4.4]nonane-2,4-dione The trans-substituted mono-alkylated product was also isolated after successive purification by flash chromatography, eluting with 40% ethyl acetate/ cyclohexane: m.p. 151 - 153°C. Analysis Calc. for $C_{26}H_{30}N_2O_6S$: C 62.63, H 6.07, N 5.62, S 6.43; found : C 62.70, H 6.20, N 5.67, S 6.51.

EXAMPLE 28

Methyl *cis*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)sulfonylaminocarbonylamino]cyclopentane-1-carboxylate and *cis*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)sulfonylaminocarbonylamino]cyclopentane-1-carboxylic acid

Methyl *cis*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylate and *cis*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylic acid

Sodium methoxide treatment of *cis*-7-(3-cyclopentyloxy-4-methoxyphenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4.4]nonane-2,4-dione, followed by flash chromatography, provided a foam.

Analysis Calc. for $C_{27}H_{34}N_2O_7S$: C 61.11, H 6.46, N 5.28; found: C 60.93, H 6.60, N 5.20.

Also isolated was *cis*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)sulfonylaminocarbonylamino]cyclopentane-1-carboxylic acid as a foam.

EXAMPLE 29

Methyl *trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)sulfonylaminocarbonylaminolcyclopentane-1-carboxylate and *trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)sulfonylaminocarbonylaminolcyclopentane-1-carboxylic acid

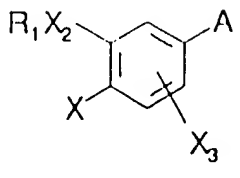
Methyl *trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylaminolcyclopentane-1-carboxylate and *trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylaminolcyclopentane-1-carboxylic acid

Sodium methoxide treatment of *trans*-7-(3-cyclopentyloxy-4-methoxyphenyl)-3-[(4-methylphenyl)sulfonyl]-1,3-diazaspiro[4.4]nonane-2,4-dione, followed by flash chromatography, provided a foam. Analysis Calc. for $C_{27}H_{34}N_2O_7S \cdot 1/4H_2O$: C 60.60, H 6.50, N 5.23; found: C 60.26, H 6.48, N 5.14.

Also isolated was *trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)sulfonylaminocarbonylamino]cyclopentane-1-carboxylic acid as a foam.

CLAIMS:

1. A compound of the formula:



(I)

wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens; C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group; C_{4-6} cycloalkyl containing one or two unsaturated bonds; C_{7-11} polycycloalkyl, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_m$-R_{10}, -$(CR_{14}R_{14})_nC(O)$-O-$(CR_{14}R_{14})_r$-R_{11}, -$(CR_{14}R_{14})_xOH$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_sO(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-$R_{10}$, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_r$-$R_{11}$, -$(CR_{14}R_{14})_y$-$R_{11}$ or -$(CR_{14}R_{14})_z$-R_{10};

X_2 is O or NR_{14};

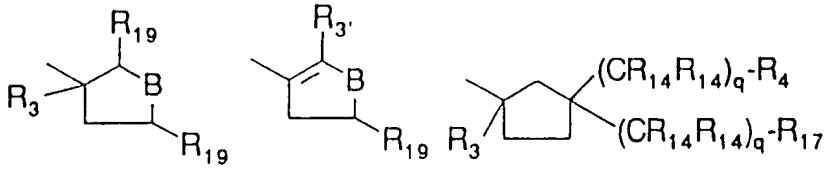
X_3 is hydrogen or X;

X is YR_2, halogen, nitro, $NR_{14}R_{14}$ or formamide;

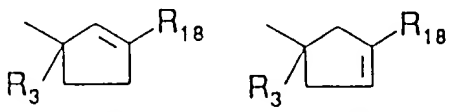
Y is O or S(O)m;

R_2 is -CH_3 or -CH_2CH_3, each may be unsubstituted or substituted by 1 to 5 fluorines;

A is:



(a) (b) (c)



(d) or (e)

B is >C=Z or C=S;

R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, OR_5, -CH_2OR_5, -NR_5R_{16}, -$CH_2NR_5R_{16}$, -$C(O)OR_5$, -$C(O)NR_5R_{16}$, -$CH=CR_9R_9$, -$C\equiv CR_9$ or -C(Z')H;

$R_{3'}$ is hydrogen, halogen, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, -CN, $-CH_2OR_5$, $-CH_2NR_8R_{16}$, $-C(O)OR_5$, $-C(O)NR_8R_{16}$ or -C(Z)H;

Z is O, $NR_{8'}$, NOR_8, NCN, NNR_8R_{16}, $C(-CN)_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_8R_{16}$, $C(-CN)NO_2$, $C(-CN)C(O)OR_{12}$ or $C(-CN)C(O)NR_8R_{16}$;

Z' is O, NR_{12}, NOR_5, NCN, $C(-CN)_2$, CR_5NO_2, $CR_5C(O)OR_5$, $CR_5C(O)NR_5R_5$, $C(-CN)NO_2$, $C(-CN)C(O)OR_{12}$ or $C(-CN)C(O)NR_5R_5$;

R_4 is E or Q;

E is OR_8, $OC(O)R_8$, $OC(O)NR_5R_8$, $OS(O)_2NR_5R_8$, $OS(O)_2R_{8'}$, SR_8, $S(O)_{m'}R_{8'}$, $S(O)_2NR_8R_{16}$, NR_8R_{16}, $NR_8C(O)R_5$, $NR_{16}C(Y')R_8$, $NR_{16}C(O)OR_{8'}$, $NR_{16}C(Y')NR_8R_{16}$, $NR_{16}S(O)_2NR_8R_{16}$, $NR_{16}C(NCN)NR_8R_{16}$, $NR_{16}S(O)_2R_{8'}$, $NR_{16}C(CR_5NO_2)NR_8R_{16}$, $NR_{16}C(NCN)SR_{12}$, $NR_{16}C(CR_5NO_2)SR_{12}$, $NR_{16}C(NR_{16})NR_8R_{16}$, $NR_{16}C(O)C(O)NR_8R_{16}$, $NR_{16}C(O)C(O)OR_8$ or $NR_{16}C(O)NR_{16}S(O)_2$(4-methylphenyl);

Q is $C(Y')R_8$, $C(O)OR_8$, $C(Y')NR_8R_{16}$, $C(CR_5NO_2)NR_8R_{16}$, $C(CR_5NO_2)SR_{12}$, $C(NR_8)NR_8R_{16}$, CN, $C(NOR_5)R_8$, $C(NOR_8)R_5$, $C(NR_5)NR_8R_{16}$, $C(NR_8)NR_5R_5$, $C(NCN)NR_8R_{16}$, $C(NCN)SR_{12}$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4- or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4- or 5-thiazolidinyl) or (2-, 4- or 5-imidazolidinyl), wherein all of the heterocylic ring systems may be optionally substituted, where possible, one or more times by $R_{8'}$;

Y' is O or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is R_5, $-C(O)R_5$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-C(NCN)S(R_{12})$ or $-C(NCN)NR_5R_{16}$;

R_7 is OR_5, $-NR_5R_{16}$ or R_{12};

R_8 is hydrogen or $R_{8'}$;

$R_{8'}$ is $-(CR_{14}R_{14})_m$-D;

D is C_{1-6} alkyl, phenyl, (2-, 3- or 4-pyridyl), 4-morpholinyl, 4-piperidinyl, (1-, 2-, 4- or 5-imidazolyl), (2- or 3-thienyl), (2- or 5-pyrimidyl) or (4- or 5-thiazolyl), triazolyl, quinolinyl or naphthyl all of which may be unsubstituted or substituted by one or more: Br, F, Cl, NR_5R_{16}, NR_6R_{16}, NO_2, $-COR_7$, $-S(O)_mR_{12}$, CN, OR_5, $-OC(O)NR_5R_{16}$, (1- or 1-(R_5)-2-imidazolyl), $-C(NR_{16})NR_5R_{16}$, $-C(NR_5)$-SR_{12}, $-OC(O)R_5$, $-C(NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}$-C(O)-R_{15}, oxazolyl, thiazolyl,

pyrazolyl, triazolyl or tetrazolyl, or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_9 is hydrogen, F or R_{12};

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted aryloxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, furanyl, pyranyl, thienyl, thiopyranyl, (3- or 4-tetrahydrothiopyranyl), 3-tetrahydrofuranyl, 3-tetrahydrothienyl, C_{3-6} cycloalkyl or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyranyl or 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl or 2-tetrahydrothienyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is $-C(O)C_{1-4}$ alkyl, unsubstituted or substituted by one or more halogens, oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5, or when R_8 and R_{16} are as NR_8R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_{17} is R_5 or Q;

R_{18} is Q, $S(O)_2R_8'$, OR_8', $OC(O)NR_8R_{16}$ or NR_8R_{16};

each R_{19} is independently hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, OR_5, $-CH_2OR_5$, $-NR_5R_{16}$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$, $-CH=CR_9R_9$, $-C\equiv CR_9$ or $-C(Z)H$;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

s is an integer from 2 to 4;

x is an interger from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

provided that

1) when R_{10} is OH in -$(CR_{14}R_{14})_n$-C(O)O-$(CR_{14}R_{14})_m$-R_{10}, -$(CR_{14}R_{14})_n$-$(C(O)NR_{14})$-$(CR_{14}R_{14})_m$-R_{10} or -$C(R_{14}R_{14})_s$O$(CR_{14}R_{14})_m$-R_{10}, then m is 2;

2) that when X_2 is O, R_3 is hydrogen and B is >C=O or >C=S, then one of the two R_{19} terms in radical (a) of term A is not hydrogen;

3) when X_2 is O, R_3 is hydrogen and B is >C=O or >C=S, then either $R_{3'}$ or R_{19} in radical (b) of term A is not hydrogen;

4) when X_2 is O, R_{17} is hydrogen, both of the q terms are zero and R_4 is OH, OC_{1-6}alkyl or SC_{1-6}alkyl in radical (c) of term A, then R_3 is other than hydrogen;

5) when term A is radical (c), Q is CN and both of the q terms are zero, then R_4 is not OH, SH or NR_8R_{16}; or

a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein R_1 is C_{4-6}cycloalkyl, CHF_2, CH_2cyclopropyl, or CH_3.

3. A compound of claim 2 wherein Y and X_2 are oxygen.

4. A compound of claim 3 where R_2 is methyl or CF_2H.

5. A compound of claim 4 where R_3 is hyrogen, CFH_2, C≡CR or -CN.

6. A compound of claim 5 where A is (a), (b), (c), (d) or (e) and B is C=O or $C=CR_5C(O)OR_5$ in (a) or (b).

7. A compound of claim 6 where $R_{3'}$ and R_{19} are independently H, C_{1-3}alkyl or $COOC_{1-3}$alkyl.

8. A compound of claim 6 where A is (c), both of q are 0, R_{17} is H and R_4 is -CN, $C(O)OR_5$, $C(O)NR_5R_8$, NR_5R_5, $NC(O)R_5$ or tetrazol-5-yl.

9. A compound of claim 6 where A is (c), both of q are 0, R_{17} is $COOR_5$ or $C(O)NR_5R_5$ and R_4 is $C(O)OR_5$, $C(O)NR_5R_5$, NR_5R_5 or $C(O)NR_{16}S(O)_2$(4-methylphenyl).

10. A compound of claim 6 where R_{18} is $C(O)R_5$, $C(O)OR_5$ or $C(O)NR_5R_5$.

11. A compound of claim 6 where A is (c), q is 0, and R_{17} is H in $C(R_{14}R_{14})R_{17}$ and q is 1, R_{14} is H and R_4 is $COOR_5$. in $C(R_{14}R_{14})_qR_4$.

12. A compound of claim 1 selected from the group consisting of:

methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate;

methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylate;

3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid;

4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxylic acid;

methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate;

N,N-dimethyl-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide;

N,N-dimethyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide;

N,N-dimethyl-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxylate;

3-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclopentene-1-carboxamide;

4-(3-cyclopentyloxy-4-methoxyphenyl)-1-cyclo-pentene-1-carboxamide;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxamide;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylic acid;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxylic acid;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1,1-dicarboxamide;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentanecarbonitrile;

5-[3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentyl]tetrazole;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentylamine;

3-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylcyclopent-2-en-1-one;

3-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylcyclopentan-1-one;

methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-3-en-2-one carboxylate;

methyl 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate;

3-(3-Cyclopentyloxy-4-methoxyphenyl)1-carboxylic acid;

3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentanecarbonitrile;

5-[3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentyl]tetrazole;

methyl 4-(3-cyclopentyloxy-4-methoxyphenyl)cyclopent-3-en-2-one carboxylate;

methyl [3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentan-1-ylidine]acetate;

1-acetamido-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane;

N-(4-acetylaminophenyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentanecarboxamide;

N-(acetylaminobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenyl)-cyclopentanecarboxamide 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-(4-pyridinylmethyl)cyclopentane-1-carboxamide;

1-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)cyclopentane-1-carboxylate;

methyl *cis*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylate;

cis-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylic acid;

methyl *trans*-3-(3-cyclopentyloxy-4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonylaminocarbonylamino]cyclopentane-1-carboxylate; and

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08609

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C49/753; C07C69/757; C07C62/34; C07C235/40
A61K31/12; A61K31/215; A61K31/195; A61K31/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; A61K ; C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,A	WO,A,9 115 451 (SMITHKLINE BEECHAM PHARMA GMBH) 17 October 1991 see claims; examples 1,2,7-13	1-16

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 JANUARY 1993	01. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SEUFERT G.H.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/08609

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 14-16 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9208609 SA 65982

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/01/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9115451	17-10-91	AU-A- 7670991	30-10-91